REMARKS

Claims 1-20, 23 and 25-37 were pending in the subject application. By this Amendment applicants have amended claims 1, 9, 14, 23, 31, 34, 35, and 36. Accordingly, claims 1-20, 23 and 25-37 are pending in the subject application.

Rejection under 35 U.S.C. § 112, first paragraph

On page 2 of the July 2, 2002 Office Action, the Examiner rejected claims 1-20, 23 and 25-37 under 35 U.S.C. § 112, first paragraph alleging that the specification, while being enabling for the specific eutectic mixtures disclosed in the examples beginning at page 10, does not reasonably provide enablement for a eutectic mixture of first and second pharmacologically active agents. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims; and the specification fails to provide information that would allow the skilled artisan to practice the invention without undue experimentation. The Examiner also stated that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity, and alleged that applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

In response, applicants admit to some confusion with respect to the sole reason given by the Examiner for questioning enablement; the Examiner stated that "the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity". Applicants, however, are not claiming new drugs or "pharmaceuticals" which require

testing of physiological activity, but rather a new composition of known pharmaceuticals. The known pharmaceuticals contemplated for use in applicants' invention have known "physiological activity". Combining such known pharmaceuticals as disclosed by applicants in their specification results in the claimed invention, i.e. a "process of making" the invention is provided in satisfaction of 35 U.S.C. § 112, first paragraph. The claimed invention is then used to treat or protect against indications the "pharmaceuticals" are known to treat or protect against, i.e. a process of "using" the invention is provided in satisfaction of 35 U.S.C. § 112, first paragraph. Accordingly, the requirements of 35 U.S.C. § 112, first paragraph, are satisfied and the enablement rejection is improper and should be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

On page 3 of the July 2, 2002 Office Action, the Examiner rejected claims 1-20, 23 and 25-37 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner alleged that claims 1-20, 23 and 25-37 are vague and indefinite because it is unclear what applicants intend by the phrases, "pharmacologically desirable" and "desirable for transdermal permeation". The Examiner also alleged that claims 9, 31, 34 and 35 are indefinite because these claims exclude a co-solvent and an additional oil phase, whereas claims 1 and 23 do not recite a solvent or oil phase. The Examiner inquired to what solvent and oil phase would these excluded ingredients be in addition.

In response, applicants have removed the objected to phrases and amended the claims to more clearly define their invention. Accordingly, the rejections under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Rejection under 35 U.S.C. § 103

In Section 11 of the July 2, 2002 Office Action, the Examiner rejected claims 1-9, 11, 12, 14-20 and 25-37 under 35 U.S.C. § 103(a) as allegedly unpatentable over US 5,206,021 (021). The Examiner alleged that US '021 is directed to oil-in-water emulsions that contain pesticidal substances and can be used for topical application to crops using a spray mixture, referring to title and col. 15, lines 22-27. The Examiner then stated that at column 8, line 65 to column 9, line 13, US '021 disclosed that the compositions may be in the form of a eutectic mixture of lipophilic pesticidal substances, and the melting point of the eutectic mixture is generally between about -20° and 30°C, which is encompassed by the instantly claimed range of less than 40°C melting point of the eutectic mixture. The Examiner then proceeded to apply the reference to the remaining rejected claims.

Initially, applicants note that they have previously addressed a rejection based on the '021 patent in their Amendment dated May 20, 2002. The Examiner, however, did not find applicants' arguments persuasive, stating that neither preamble use nor inherent properties render a claim to a composition patentable over the prior art composition. The Examiner also stated that the '021 patent is directed to pesticidal compositions that are topically applied to crops, and that topical application of the composition to crops would result in topical application to the pests, which would lead to penetration of

the pesticides into the pests. The Examiner alleged that pesticidal compositions are also topically applied to humans for the same purpose.

In response, applicants, wish to clarify that their composition is formulated for enhanced "transdermal permeation" as recited in the composition claims. Furthermore, applicants are also claiming a method for "enhancement of dermal permeation". One would certainly not apply "pesticidal compositions" to animals or humans for dermal permeation. Applicants further discuss this below.

The Examiner also noted applicants' argument that pesticides are not pharmaceutically acceptable. However, the Examiner proceeded to assert that the term "pharmacologically active" is interpreted as encompassing any substance that has therapeutic activity, and that the lipophilic substances disclosed by the '021 patent at column 9, line 25 to column 12, line 40 are encompassed by these definitions. The Examiner then alleged that applicants have not provided any evidence of record that the lipophilic substances of US '021 are not pharmaceutically acceptable or pharmacologically active. The Examiner then alleged that pesticides are drugs, referring to definition number (3) of the word, "drug" found in Merriam-Webster's Collegiate Dictionary, 10th Ed., Merriam-Webster, Inc. Springfield, MA (1998), page 355, which states, "a substance other than food intended to affect the structure or function of the body." The Examiner took the position that the pesticides of US '021 are intended to affect the function of the body of the pests at which they are targeted.

In response, applicants point out that they have indeed

provided a definition of the term "pharmacological agent" on page 6, lines 17-19 of their disclosure. Specifically, the term is defined as an "agent used in prophylaxis or therapy of any condition affecting the health of the human or animal species." Of note are the terms "prophylaxis" and "therapy" which cannot include pesticides because pesticides are clearly detrimental to human and animal health as discussed at length in applicants' May 20, 2002 Amendment, and which is incorporated herein by reference. A definition of these two terms consistent with applicants' usage is found in Merriam-Webster's Collegiate Dictionary.

Applicants further note that another definition of 'drug' provided by Merriam-Webster's Collegiate Dictionary, relied upon by the Examiner, is entirely consistent with applicants' usage as a prophylactic and therapeutic, see, e.g., page 360, 'a medicinal substance. The agents of the '021 patent are not drugs as defined in applicants' specification. Indeed, many of the '021 agents are toxic to humans, hence the widespread concern about pesticide toxicity and damage to human health. Applicants, therefore, submit that the teachings of the '021 patent are a positive **disincentive** to one skilled in the art to consider any teaching of the '021 patent as motivating the claimed invention.

It is well settled that terms in a claim should be interpreted using the specification. According to applicants' specification, it is clear that applicants' use of the terms "pharmacologic" or "pharmacologically" excludes the pesticides of the '021 patent. Furthermore, applicants' clear and unambiguous statements in this and their previous Amendment, both of which forming a part of the record of this

application, that pesticides are not within the scope of their invention should be given credence. Notwithstanding the foregoing, applicants have amended the claims to bring the definition of the specification into the claims. Accordingly, the pesticides of the '021 patent are not included within the scope of applicants' claims, and any rejection based on this reasoning is improper and should be withdrawn.

Applicants also wish to point out that their composition claims and their method claims are patentable on independent grounds. For example, as the Examiner noted, a composition cannot derive patentability by reciting an intended use. However, a method can. Applicants' method claims, e.g. claim 23, recite a "method for mutual enhancement of dermal permeation", which method is certainly not applicable for use with pesticides, as alluded to above. Applicants' composition claims, as amended, recite that the components of the composition are prophylactic or therapeutic agents, i.e. not pesticides.

Applicants' method claims recite administration to an accessible body surface of an animal species and further require application of a 'topical composition' to any accessible body surface. The term 'body surface' clearly means, in the context of this application, the human or animal body. Thus, the Examiner's linking of the '021 patent, where the pesticidal compositions are applied to crops, cannot be relevant prior art. In particular, the Examiner's argument that topical application to pests leads to penetration into pests, and the equating of this to the human or animal situation, is unreasonably tortuous and provides no incentive to those skilled in the art to make the connection leading to

the present invention. Given that the agents in the '021 patent do not encompass within them the concept of safety (lack of toxicity) in human and animal use, it will be understood by those skilled in the art that the terms "prophylactic" or "therapeutic" completely exclude the agents of the '201 patent. Indeed, since the whole focus of pesticide use via topical contact is to restrict absorption of the pesticide into the plant due to the perceived toxicity of pesticides, applicants submit that the '021 document provides a **dis**incentive to one skilled in the art to arrive at the present invention.

Bringing the foregoing into the context of the requirements for a *prima facie* case of obviousness, applicants point out that the '021 patent provides neither the motivation, nor the expectation of success, nor all of the elements recited in applicants' claims. Specifically, the '021 patent does not motivate one skilled in the art to make a composition that has enhanced transdermal permeation properties, or a method of use of such a composition because transdermal permeation is not even mentioned in the '021 patent. Certainly, the '021 patent does not teach how to enhance dermal permeation of pharmacologically active agents as recited in applicants' method claims. Clearly, there is no teaching in the '021 patent that eutectic mixtures provide mutually enhanced transdermal permeation, i.e the '021 does not as it cannot provide the expectation of success of applicants' invention. Finally, the '021 patent fails to provide all of the elements recited in applicants' claims, e.g. the pharmacologically active agents, as defined by applicants, and as recited in the dependent claims, are not found in the '021 patent. Accordingly, the '021 patent does not support a *prima facie*

case of obviousness.

Rejection under 35 U.S.C. § 103 - claim 10

In Section 12 of the July 2, 2002 Office Action, the Examiner rejected claim 10 under 35 U.S.C. 103(a) as allegedly unpatentable over US 5,206,021 (021) as applied to claims 1-9, 11, 12, 14-20 and 25-37 above, and further in view of either the USPATFULL abstract of US 5525597 (597) or the CAPLUS abstract of WO 9518122 (122). The Examiner alleged that US '021 teaches all the limitations of the claims as stated in the 35 U.S.C. 103(a) rejection above, but acknowledged that it does not teach the pharmacologically active agents of claim 10. However, the Examiner alleged that US '597 teaches that capsaicin enhances the effectiveness of insecticidal compositions and WO '122 teaches that synergistic combinations of insecticides can be obtained with the addition of triclosan.

In response, applicants point out that the primary reference, US '021, has been addressed above. The additional two references also relate to pesticides, and in any event do not remedy the deficiencies of the '021 patent, as discussed below.

The 597 document and the 122 document neither disclose nor suggest the use of therapeutic or prophylactic agents. Instead, they each deal with pesticides. A pesticide is something which, in medical or veterinary terms, **destroys or controls** unwanted species of plants or animals. Furthermore, both the 597 document and the 122 document neither disclose nor suggest the use of eutectic mixtures to achieve mutually enhanced permeation of any agent, much less therapeutic or

prophylactic agents. There is not a single mention in either of the 597 document or the 122 document of eutectic mixtures at all!

The term "synergy" or "synergism" used in the 597 document and the 122 document means "the combined effects of two or more drugs that exceeds the sum of their individual effects" (Concise Oxford English Dictionary 1990, p1237). "Synergism" arises if the activity of two agents in combination is greater than the sum of their separate activities. "Synergism" also arises, as in US 5,525,597 (597 document), when one compound, although not active as an insecticide itself (see column 6, line 59-60, enhances the insect killing activity of another compound.

Applicants submit that the Examiner's arguments concerning the "synergistic" effects noted in the 122 and 597 documents are not relevant to the present invention. Specifically, the term "synergy" in these documents refers to an enhancement involving a biological interaction of the compounds at an active site in the body. This is entirely consistent with the 597 document (at column 6, line 58), where insecticide "activity-enhancing" and "synergistic" effects are taken to have the same meaning.

This is quite different from the claimed invention, in which there must be a physical effect in the composition to be applied, i.e. the at least two agents must form a eutectic mixture in the composition to be applied, the unexpected result of which is mutual enhancement of the ability of both agents to cross a biological barrier membrane, i.e. skin, en route to their respective target site(s) of action in the

body. This mutual enhancement of transdermal permeation is completely unrelated to their subsequent mechanisms of action. Applicants' claimed mutual enhancement of transdermal permeation effect provides a means of delivering **more** of each drug into the body. In summary, the present invention concerns itself with mutually enhanced delivery of agents in a eutectic mixture to achieve greater concentrations in the body but does not concern itself with any subsequent biological event after that absorption into the body.

Accordingly, the cited references, alone or in combination do not support a *prima facie* case of obviousness.

Rejection under 35 U.S.C. § 103 - claim 13

In Section 13 of the July 2, 2002 Office Action, the Examiner rejected claim 13 under 35 U.S.C. 103(a) as allegedly unpatentable over US 5,206,021 (021) as applied to claims 1-9, 11, 12, 14-20 and 25-37 above, and further in view of The Condensed Chemical Dictionary, 10th Ed., Gessner G. Hawley (ed.), Van Nostrand Reinhold Co., New York, (1981), pages 252, 602 and 603. The Examiner alleged that US '021 teaches all the limitations of the claims as stated in the 35 U.S.C. 103(a) rejection above, but acknowledged that it does not teach the pharmaceutically acceptable component of instant claim 13. However, the Examiner alleged that Hawley teaches that one of the common uses of lauric acid is as an insecticide (pages 602-603), and Hawley also teaches that cinnamic acid is an anthelmintic, a compound that works against helminths (parasitic worms).

In response, applicants point out that the primary reference, US '021, has been addressed above. The additional Hawley

reference does not remedy the deficiencies of the '021 patent.

Hawley discloses that lauric acid and cinnamic acid are an insecticide and an anthelmintic, respectively. However, neither lauric acid nor cinnamic acid is a prophylactic or a therapeutic agent as is defined in the subject specification. Anthelminthic or insecticidal activity has the effect of killing the insect or the parasitic intestinal worm to which it is applied. Given the comments above on the disincentive provided by, and lack of relevance of the '021 patent, the nature of these two agents, in any case, is not relevant to the context of the present invention.

Conclusion

In view of applicants amendment of the claims and remarks above, applicants respectfully submit that the rejections set forth in the July 2, 2002 Office Action should be withdrawn. Applicants also draw the Examiner's attention to the secondary considerations which are supportive of a finding of non-obviousness. Specifically, the inventors overcame a technical prejudice in the art which conventionally considered, at the time the invention was made, that the formation of eutectic mixtures is undesirable, as discussed at page 2, lines 3-19 of the specification. In addition, the at least two pharmacologically active agents of the eutectic mixture of the discontinuous phase support each other in their effects so that a new technical result is achieved. Specifically, mutual enhancement of transdermal permeation of each of the first and second pharmacologically active agents was observed and was exemplified and this could not have been predicted from the known properties of each of the individual active agents. Applicants submit that this is a surprising synergistic

effect, which is clearly exemplified in the examples and corresponding figures.

No fee, other than the enclosed $920.00 extension of time fee, is deemed necessary in connection with the filing of this Response. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Jay H. Maioli
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Date 12.27.02

ATTACHMENT A
CLAIMS AS AMENDED WITH MARKINGS TO SHOW CHANGES
SERIAL NO. 09/423,715

1. (Twice Amended) A topical ~~pharmacologically desirable, pharmaceutically acceptable~~ composition for mutual enhancement of transdermal permeation of at least a first and a second pharmaceutically acceptable components which are both pharmacologically active agents, the composition comprising

an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase comprising a eutectic mixture of first and second pharmacologically active agents ~~that are desirable for transdermal permeation~~ and the continuous phase comprising a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and

at least one compatible emulsifying agent,

~~with the provisos that~~ wherein when the first pharmacologically active agent is a local anesthetic, the second pharmacologically active agent is not a local anaesthetic ~~or~~, wherein when the second pharmacologically active agent is a local anesthetic, the first pharmacologically active agent is not a local anesthetic, and wherein the first and the second pharmacologically active agents are each a prophylactic or a therapeutic agent.

2. The topical composition according to Claim 1, in which the first pharmacologically active agent has a melting point between 35 and 75°C, and the second pharmacologically active agent has a melting point

between -40°C and 150°C.

3. The topical composition according to Claim 1, in which the topical composition additionally includes, in the eutectic mixture, a third pharmaceutically acceptable component.

4. The topical composition according to Claim 3, in which the third pharmaceutically acceptable component has a melting point between 40 and 150°C.

5. The topical composition according to Claim 3 or 4, in which the third component is a third pharmacologically active agent.

6. The topical composition according to Claim 3, in which the topical composition additionally includes, in the eutectic mixture, a fourth pharmaceutically acceptable component.

7. The topical composition according to Claim 6, in which the fourth pharmaceutically acceptable component has a melting point between 40 and 150°C.

8. The topical composition according to Claim 6 or 7, in which the fourth component comprises a fourth pharmacologically active agent.

9. (Amended) The topical composition according to Claim 1, in which said at least one discontinuous phase consists essentially of the eutectic mixture ~~contains no co-solvent or additional oil phase, so that the eutectic~~

~~mixture substantially comprises the or each discontinuous phase of the emulsion~~.

10. The topical composition according to Claim 1, in which the first pharmacologically active agent is selected from the group consisting of triclosan, chlorocresol, chlorbutanol, methyl nicotinate, triprolidine, promethazine, trimeprazine, sulfiram, oxybutynin, capsaicin, testosterone enanthate and choline salicylate.

11. The topical composition according to Claim 1, in which the second pharmacologically active agent is selected from the group consisting of non-steroid anti-inflammatory arylpropionic agents, narcotic analgesics, anti-fungal agents, antibacterial agents, anticholinergics, anthelmintics, antihistaminics, and antihypertensives.

12. The topical composition according to Claim 8, in which the third and fourth pharmacologically active agents are each selected from the group consisting of non-steroid anti-inflammatory agents, narcotic analgesics, anti-fungal agents, antibacterial agents, anticholinergics, antihypertensives, antihistaminics, and anthelmintics.

13. The topical composition according to Claim 3 or 4, in which the third pharmaceutically acceptable component is lauric acid, stearyl alcohol, menthol, thymol, cinnamic acid or an ester thereof.

14. (Amended) The topical composition according to Claim 1, in which the pharmaceutically acceptable carrier is

substantially hydrophilic, said carrier comprising ~~containing~~ substantially water as the continuous phase.

15. The topical composition according to Claim 1, in which the pharmaceutically acceptable carrier contains at least one gelling or suspension agent.

16. The topical composition according to Claim 15, in which the gelling or suspension agent is selected from the group consisting of carbomers, modified celluloses, naturally-occurring synthetic or semi-synthetic gums, modified starches, co-polymers formed between maleic anhydride and methyl vinyl ether, colloidal silica and methacrylates or a mixture thereof.

17. The topical composition according to Claim 1, in which the topical composition is in the form of a gel, lotion, suspension, cream, aerosol spray, transdermal patch, medicated dressing or soft gelatin capsule.

18. The topical composition according to Claim 1, in which the emulsifying agent is selected from the group consisting of non-ionic, cationic and anionic surfactants.

19. The topical composition according to Claim 18, in which the emulsifying agent is a non-ionic surfactant.

20. The topical composition according to Claim 1, in which the at least two pharmacologically active agents are structurally and/or pharmacologically diverse.

23. (Twice Amended) A method for mutual enhancement of dermal permeation of at least a first and a second pharmaceutically acceptable components which are both pharmacologically active agents, the method comprising

applying a topical composition for mutual enhancement of transdermal permeation of at least first and second pharmacologically active agents, the composition comprising

an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase comprising a eutectic mixture of first and second pharmacologically active agents and the continuous phase comprising a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent,

~~with the provisos that,~~ wherein when the first pharmacologically active agent is a local anesthetic, the second pharmacologically agent is not a local anesthetic, ~~or,~~ wherein when the second pharmacologically active agent is a local anesthetic, the first pharmacologically active agent is not a local anesthetic, and wherein the first and the second pharmacologically active agents are each a prophylactic or a therapeutic agent,

to an accessible body surface of an animal.

25. The topical composition according to claim 2, wherein the first pharmacologically active agent has a melting point between 40 and 50°C, and the second pharmacologically active agent has a melting point between -5 and 90°C.

26. The topical composition according to claim 4, wherein the third pharmaceutically acceptable component has a melting point between 40 and 75°C.

27. The topical composition according to claim 7, wherein the fourth pharmaceutically acceptable component has a melting point between 40 and 75°C.

28. The topical composition according to claim 11, wherein the second pharmacologically active agent is selected from the group consisting of triclosan, chlorocresol, capsaicin, trimeprazine, choline salicylate, methyl nicotinate, ibuprofen, ketoprofen, fenoprofen, flurbiprofen, etodolac, fentanyl, econazole, ketoconazole, mupirocin, chlorbutanol, clindamycin, iodine, oxybutynin, tetramisole, triprolidine, promethazine, and propranolol.

29. The topical composition according to Claim 12, wherein the third and fourth pharmacologically active agents are each selected from the group consisting of triclosan, chlorocresol, capsaicin, trimeprazine, choline salicylate, methyl nicotinate, ibuprofen, ketoprofen, fenoprofen, flurbiprofen, etodolac, fentanyl, econazole, ketoconazole, mupirocin, chlorbutanol, clindamycin, iodine, oxybutynin, propranolol, triprolidine, promethazine, and tetramisole.

30. The topical composition according to Claim 16, wherein the gelling or suspension agent is selected from the group consisting of xanthan gum, acacia, tragacanth, and a mixture thereof.

31. (Amended) The topical composition according to Claim 9, in which said at least one discontinuous phase consists of the eutectic mixture ~~contains no co-solvent or additional oil phase, so that the eutectic mixture essentially consists of the or each discontinuous phase of the emulsion~~.

32. The topical composition according to Claim 14, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier essentially consisting of water as the continuous phase.

33. The method of claim 23, wherein the animal is a human.

34. (Amended) The method according to Claim 23, in which said at least one discontinuous phase consists essentially of the eutectic mixture ~~contains no co-solvent or additional oil phase, so that the eutectic mixture substantially comprises the or each discontinuous phase of the emulsion~~.

35. (Amended) The method according to Claim 34, in which said at least one discontinuous phase consists of the eutectic mixture ~~contains no co-solvent or additional oil phase, so that the eutectic mixture essentially consist of the or each discontinuous phase of the emulsion~~.

36. (Amended) The method according to Claim 23, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier comprising ~~containing~~ substantially water as the continuous phase.

37. The method according to Claim 36, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier essentially consisting of water as the continuous phase.